

REMARKS

Claims 1-35 appear in this application for the Examiner's review and consideration.

Claims 1-35 have been rejected in the April 30, 2007 Office Action. This Action has been made Final.

Applicants traverse each and every objection.

Objection

The Final Office Action of April 30, 2007 states on page 2 in paragraph no. 2, that the objection previously made to the specification is maintained. However, the Applicants respectfully submit that no objection was made to the Specification in the previous Office Action of October 4, 2006. Furthermore, no objection is indicated on the Office Action Summary (form PTOL-326), for either the present Office Action, dated April 30, 2007 or the previous Office Action, dated October 4, 2006.

Nevertheless, the Specification has been read for errors. Applicants are not aware of any errors in the Specification at this time. However, Applicants reserve the right to correct errors to the Specification, Drawings and Abstract, if any errors are later realized.

Rejection under 35 U.S.C. § 103 (a)

Claims 1-35 were rejected under 35 U.S.C. § 103 (a) as allegedly obvious over U.S. Patent No. 5,149,538 to Granger *et al.* ("Granger"). Applicants respectfully traverse this rejection.

A finding of obviousness under 35 U.S.C. § 103 requires a determination of: (1) the scope and content of the prior art, (2) the level of ordinary skill in the art, (3) the difference between the claimed subject matter and the prior art, and (4) whether the differences are such that the subject matter as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made. *Graham v. Deere* 383 U.S. 1, 17 (1966). Therefore, obviousness inquiries require determining whether the prior art suggests the claimed invention and whether that prior art would have indicated a reasonable expectation of success to one of ordinary skill in the art. *In re O'Farrell*, 853 F.2d 894, 902-903, 7 USPQ2d 1673, 1680-1681 (Fed. Cir. 1988).

Proof of a *prima facie* case of obviousness requires proving three elements: (1) a particular reference (or combined references) must suggest or teach all the limitations of the

challenged claim, (2) a suggestion or motivation from the prior art to modify or combine the reference teachings, and (3) a reasonable expectation of success must exist from the prior art. M.P.E.P. §§2142, 2143, citing *In re Vaeck*, 947 F.2d 488, 493, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991). Care must be exercised not to use the Applicants' disclosure to fill in the gaps of the prior art. *In re Vaeck*, 947 F.2d 488, 493, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991), citing *In re Dow Chemical Co.*, 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988).

The final rejection is made under 103(a) and, therefore, asserts that after reading Granger, one skilled in the art, as of the August 20, 2002 priority filing date of the present application, would have had the knowledge and motivation to construct the invention as claimed in each of the 35 claims of the above-captioned application. However, Granger does not provide one skilled in the art with either the knowledge or the motivation to construct a device that meets all the limitation of the presently claimed invention.

Granger discloses a misuse-resistive transdermal opioid dosage form, and states “[t]he present invention overcomes the deficiencies of the prior art dosage forms by providing a transdermal dosage form containing an opioid and an opioid antagonist, wherein the opioid and the antagonist are physically separated by an impermeable barrier. This barrier prevents undesirable ion exchange and other interactions between the opioid and the antagonist.” (Granger, col. 1, ll. 59-66). As the Examiner has agreed, Granger is silent with regard to the use of an active agent and a combination of adverse agents which comprises at least one adverse agent in the form of a free base and at least one adverse agent in the form of a pharmaceutically acceptable salt of the adverse agent. (See the April 30, 2007 Office Action, page 4, ll. 4-5.)

In contrast to Granger, the present invention discloses and claims a transdermal dosage form which comprises an active agent or a pharmaceutically acceptable salt of an active agent in combination with both at least one adverse agent in the form of a free base and at least one adverse agent in the form of a pharmaceutically acceptable salt of the adverse agent. The result of the use of at least one adverse agent in base form, and at least one adverse agent in salt form is that the dosage form from which a potential abuser will attempt to extract active agent will also necessarily extract adverse agent, regardless of whether the potential abuser attempts to extract the adverse agent by using a polar solvent or a non-polar solvent. See, *inter alia*, Specification, page 6, ll. 8-20. Granger simply fails to address this problem, and does not require or suggest the use of both an adverse agent in base form and an adverse agent in salt form. In fact, Granger teaches a preferred dosage form containing

“naltrexone or salts thereof as the antagonist substance. (Granger, col. 2, ll. 65-68; *see also*, col. 5, ll. 37-38 and col. 7, ll. 43-44).

With regard to the motivation to modify Granger to include both free base and salt forms of the antagonist the April 30, 2007 Office Action states “[o]ne having ordinary skill in the art would have adjusted the ratio between salt and free base of the antagonist to obtain continuous antagonistic effect as well as pain release.” (April 30, 2007 Office Action, page 5, ll. 10-13, emphasis added.) However, this assertion is beyond the scope of Granger. Granger teaches an agonist delivery device wherein an antagonist is enclosed within an impermeable barrier. In Granger, there is no teaching of or motivation to obtain a “continuous antagonistic effect” by the use of the combination of free base and salt forms of the antagonist or otherwise. Assuming, *arguendo*, that as of the August 20, 2002 priority filing date of the present application, the Examiner is correct in the statement found on pages 8-9 of the Office Action that “the knowledge available to the skilled artisan that salts and free bases of the drugs have different solubility and bioavailability and the combination of both will provide different release time providing prolonged period of release,” still no motivation exists for one of skill in the art to use Granger to manufacture a dosage form containing at least one adverse agent in the form of a free base and at least one adverse agent in the form of a pharmaceutically acceptable salt of the adverse agent, as disclosed and claimed in the present invention.

Granger distinguishes the prior art by, *inter alia*, stating the “[t]he dosage forms of the prior art have deficiencies in that ... the narcotic and antagonist are physically combined such that adverse physical and chemical interaction may occur.” (Granger, col. 1, ll. 55-59, *see also*, col. 2, ll. 21-23.). Granger states that it “overcomes the deficiencies of the prior art dosage forms by providing a transdermal dosage form ... wherein the opioid and antagonist are physically separated by an impermeable barrier.” (Granger, col. 1, ll. 59-64.). Unlike Granger, the dosage form of the present invention may or may not have a barrier between the active agent and the adverse agents.

As the Examiner has agreed, Granger does not disclose the use of at least one adverse agent in the form of a free base and at least one adverse agent in the form of a pharmaceutically acceptable salt of the adverse agent. Further, Granger does not provide the motivation to use at least one adverse agent in the form of a free base and at least one adverse agent in the form of a pharmaceutically acceptable salt of the adverse agent in its transdermal dosage form. Accordingly, Granger does not meet the standard for a *prima facie* case of obviousness.

Claims 8 and 18

Dependent claims 8 and 18, specifically claim that the “the transdermal dosage form comprises a reservoir comprising the active agent, or a pharmaceutically acceptable salt thereof, the adverse agent in the form of a free base and the pharmaceutically acceptable salt of an adverse agent.” As discussed above, Granger teaches the compartmentalization of the agonist away from the antagonist. Whereas, claims 8 and 18 of the above-captioned application, specify the combination of the agonist and the antagonist (in both forms) in the same reservoir. This clause of both claims 8 and 18 yet further delineates the difference between Granger and the claimed invention of the above captioned application.

Conclusion

Applicants respectfully submit that in view of the above remarks, the Examiner’s rejection of claims 1-35 under 35 U.S.C. § 103 (a) over Granger has been overcome, and should be withdrawn.

In light of the above remarks, Applicants respectfully request that the Examiner reconsider this application with a view towards allowance. The Examiner is invited to call the undersigned attorney at (212) 692-1086, if a telephone call could help resolve any remaining items.

It is respectfully requested that the above remarks be entered into the file of the application. No fee is believed to be due for this response. However, the Commissioner is hereby authorized to charge any required fees to Duane Morris LLP Deposit Account No. 04-1679.

Date: July 30, 2007

Respectfully submitted,



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